

# Preparation and characterization of solid dispersion freeze-dried efavirenz - polyvinylpyrrolidone K-30

Lili Fitriani, Alianshar Haqi,  
Erizal Zaini

Department of Pharmaceutics, Faculty  
of Pharmacy, Andalas University,  
Kampus Limau Manis, Padang,  
Indonesia

*J. Adv. Pharm. Technol. Res.*

## ABSTRACT

The aim of this research is to prepare and characterize solid dispersion of efavirenz – polyvinylpyrrolidone (PVP) K-30 by freeze drying to increase its solubility. Solid dispersion of efavirenz – PVP K-30 was prepared by solvent evaporation method with ratio 2:1, 1:1, and 1:2 and dried using a freeze dryer. Characterizations were done by scanning electron microscopy (SEM), powder X-ray diffraction analysis, differential thermal analysis (DTA), and Fourier transform infrared (FT-IR) spectroscopy. Solubility test was carried out in CO<sub>2</sub>-free distilled water, and efavirenz assay was conducted using high-performance liquid chromatography with acetonitrile:acetic acid (80:20) as the mobile phases. Powder X-ray diffractogram showed a decrease in the peak intensity, which indicated the crystalline altered to amorphous phase. DTA thermal analysis showed a decrease in the melting point of the solid dispersion compared to intact efavirenz. SEM results indicated the changes in the morphology of the crystal into an amorphous form compared to pure components. FT-IR spectroscopy analysis showed a shift wavenumber of the spectrum efavirenz and PVP K-30. The solubility of solid dispersion at ratio 2:1, 1:1, and 1:2 was 6.777 µg/mL, 6.936 µg/mL, and 14,672 µg/mL, respectively, whereas the solubility of intact efavirenz was 0.250 µg/mL. In conclusion, the solubility of solid dispersion increased significantly ( $P < 0.05$ ).

**Key words:** Efavirenz, freeze dried, polyvinylpyrrolidone K-30, solid dispersion

## INTRODUCTION

Efavirenz is an antiretroviral drug class of nonnucleoside reverse transcriptase inhibitors and is used as a treatment against human immunodeficiency virus type 1 and classified as class II based on Biopharmaceutical Classification System with low solubility but high permeability.<sup>[1]</sup> Efavirenz is practically insoluble in water.<sup>[2]</sup> This will affect the solubility and dissolution rate which ultimately will affect the process of absorption and bioavailability of efavirenz

in the body. Various methods have been undertaken to improve the solubility of efavirenz such as formation of inclusion complexes with cyclodextrins,<sup>[3]</sup> manufacture of solid dispersion,<sup>[1,4]</sup> use of surfactant,<sup>[2]</sup> co-micronization,<sup>[5]</sup> and formation of eutectic mixture.<sup>[6]</sup>

Solid dispersion system is a system that consists of one or more active substances in an inert carrier or matrix in the solid state prepared by the method of solvent, melting, and combined melting and solvent.<sup>[7]</sup> In the manufacture of solid dispersion system, it is very important to understand the physicochemical properties of the drug and a suitable carrier to increase the solubility of drugs.<sup>[8]</sup> Freeze drying, also known as lyophilization, is a technique mixing the active compounds and the carrier substance which dissolved in

### Address for correspondence:

Dr. Erizal Zaini,  
Faculty of Pharmacy, Andalas University,  
Kampus Limau Manis, Padang, Indonesia.  
E-mail: erizal@ffarmasi.unand.ac.id

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10.4103/2231-4040.184592

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**How to cite this article:** Fitriani L, Haqi A, Zaini E. Preparation and characterization of solid dispersion freeze-dried efavirenz – polyvinylpyrrolidone K-30. *J Adv Pharm Technol Res* 2016;7:105-9.

the solvent. The mixture was frozen and sublimated, thus obtained results lyophilization molecular dispersion. Advantages of this technique are minimizing stress on the temperature during the process of formation of the solid dispersion of active substances as well as minimizing the risk of the occurrence of phase separation of the solution as quickly as vitrification.<sup>[8,9]</sup>

In the previous research, efforts have been made to increase the solubility and dissolution rate of efavirenz, which showed good results such as the formation of solid dispersion efavirenz-polyethylene glycol (PEG) 6000,<sup>[11]</sup> and the formation of solid dispersion efavirenz-PEG 8000 and polyvinylpyrrolidone (PVP) K-30 with drying technique using a rotary evaporator,<sup>[10]</sup> then the formation of efavirenz - hydroxypropyl methylcellulose solid dispersion by freeze drying techniques.<sup>[11]</sup> Recent study showed the dissolution rate of solid dispersion of efavirenz – PVP K-30 improved significantly by spray drying technique.<sup>[12]</sup>

Therefore, the aim of this study was to prepare solid dispersion of efavirenz – PVP K-30 and to characterize the solid dispersion by freeze drying technique. The intact and solid dispersion were characterized using powder X-ray diffraction analysis, differential thermal analysis (DTA), scanning electron microscopy (SEM), and Fourier transform infrared (FT-IR) spectroscopy analysis. The impact on the solubility of solid dispersion was determined by solubility test and measured by high-performance liquid chromatography (HPLC).

## MATERIALS AND METHODS

### Materials

Efavirenz (Kimia Farma, Indonesia), PVP K-30 (DELTA Chemical, Indonesia), 96% ethanol (Brataco Chemika, Indonesia), Acetonitrile HPLC Grade (Merck, Germany), distilled water. All materials were used as received.

### Methods

#### *Preparation of solid dispersion*

Efavirenz and PVP K-30 were mixed with a ratio of 2:1, 1:1, and 1:2. Efavirenz dissolved in 5 mL of 96% ethanol, whereas PVP K-30 was dissolved in 20 mL of distilled water. The solution was mixed on a magnetic stirrer and then homogenized. Once homogeneous, the mixture was dried using a freeze dryer (Christ Alpha 1-2 LD Plus, France) and the freeze-dried solid dispersions were stored in a sealed container and put in desiccator.

#### *Scanning electron microscopy analysis*

Sample powder was placed on the sample holder aluminum and coated with gold. The sample was observed by SEM (JEOL, JSM-6360LA, Japan) at various magnifications. The analysis was set at voltage was set at 20 kV and

the current was 12 mA. SEM analysis was conducted for intact efavirenz, PVP K-30, and solid dispersion of efavirenz – PVP K-30.

#### *Powder X-ray diffraction analysis*

Analysis of the X-ray powder diffraction was done using a diffractometer (PAN Analytical, The Netherlands). Sample was placed on pan analytical and leveled to prevent particle orientation during sample preparation. Measurement was done at conditions as follows: The target metals Cu, filter K $\alpha$ , 45 kV voltage, 40 mA current, the analysis carried out in the range of 2 theta 10–40° at room temperature. Analyses were performed for efavirenz, PVP K-30, and solid dispersion of efavirenz – PVP K-30.

#### *Differential thermal analysis*

Thermal analysis of samples was carried out using a differential thermal analyzer (Mettler Toledo FP90, Switzerland) calibrated with Indium temperature. A small amount of sample (5–7 mg) was placed on an aluminum pan. DTA temperature was programmed in a range from 30°C to 250°C with a heating rate 10°C per min. Analysis was performed for efavirenz, PVP K-30, and solid dispersion of efavirenz – PVP K-30.

#### *Fourier transform infrared spectroscopy analysis*

Samples were analyzed using an infrared spectrophotometer (Shimadzu LC-20AD, Japan) by dispersing samples on KBr plate and were compressed at high pressure (hydraulic press). Absorption spectra were recorded with FT-IR at wavenumber 4000–500 cm<sup>-1</sup>. Analyses were performed for efavirenz, PVP K-30, and solid dispersion of efavirenz – PVP K-30.

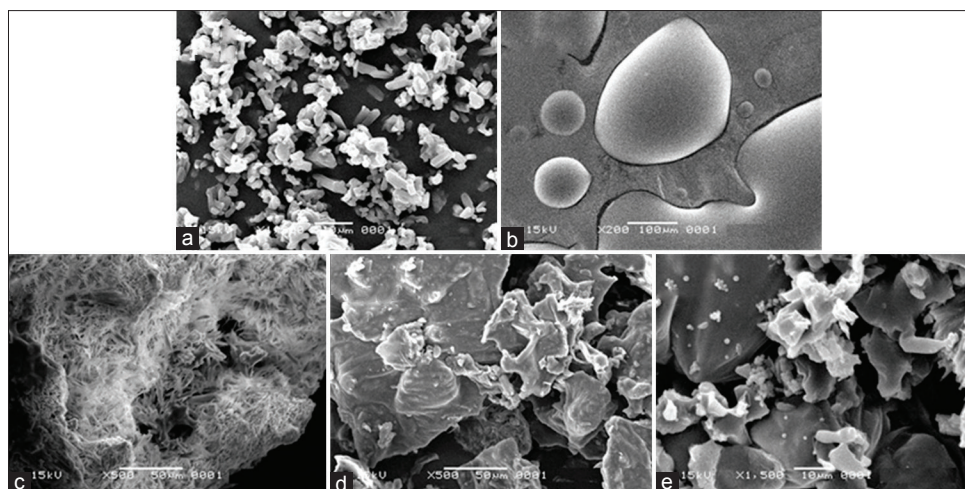
#### *Solubility test*

Solubility test was conducted on intact efavirenz and solid dispersions of efavirenz – PVP K-30. Sample was made into a saturated solution. Each formula was weighed equivalent to 100 mg of efavirenz, then put in a 100 mL Erlenmeyer flask and added 100 ml of distilled water free of CO<sub>2</sub>. Solubility test was conducted for 24 h using an orbital shaker. Samples were filtered using Whatman filter paper (0.45  $\mu$ m), and 1 mL of filtrate solution was then taken, and amount of efavirenz dissolved was measured by HPLC (Shimadzu LC-20D, Japan) with acetonitrile:acetic acid (80:20) as mobile phases.

## RESULTS

### *Scanning electron microscopy analysis*

Morphology of intact efavirenz, PVP K-30, and solid dispersion of efavirenz – PVP K-30 using the SEM is shown in Figure 1. Intact efavirenz is shown as a crystalline with a polyhedral rod-shaped crystal habit, whereas PVP K-30 is irregular round shape on its surface. The morphology of solid dispersion showed pores as



**Figure 1:** Scanning electron microscopy microphoto of (a) intact efavirenz, (b) polyvinylpyrrolidone K-30, (c) solid dispersion at ratio 2:1, (d) solid dispersion at ratio 1:1 and (e) solid dispersion at ratio 1:2

characteristic freeze drying process. Moreover, solid dispersion with different ratios showed that efavirenz was dispersed in PVP K-30 as there was no efavirenz crystal observed.

### Powder X-ray diffraction analysis

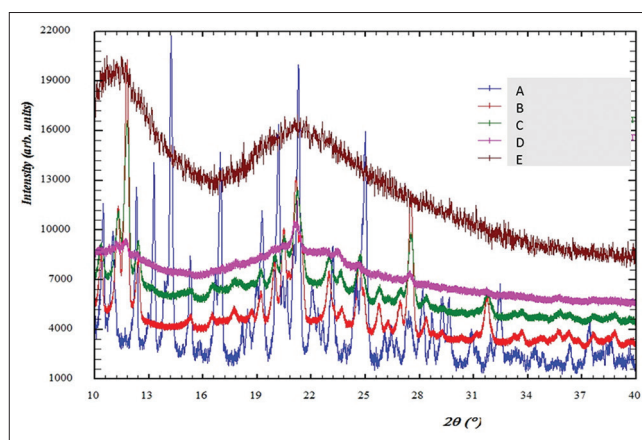
X-ray diffraction analysis of intact efavirenz, PVP K-30, and solid dispersions of efavirenz – PVP K-30 can be seen in Figure 2. The diffractogram showed that there is a decrease in the intensity of solid dispersion samples compared to intact efavirenz. The decrease in the degree of crystallinity of solid dispersion did not alter as a whole to be amorphous phase yet. Solid dispersion at ratio 2:1, which had a higher concentration of efavirenz, depicted higher crystallinity degree compared to solid dispersion at ratio 1:1 and 1:2. In contrary, solid dispersion at ratio 1:2 had the lowest degree of crystallinity as can be seen there was no sharp peak observed on the diffractogram.

### Differential thermal analysis

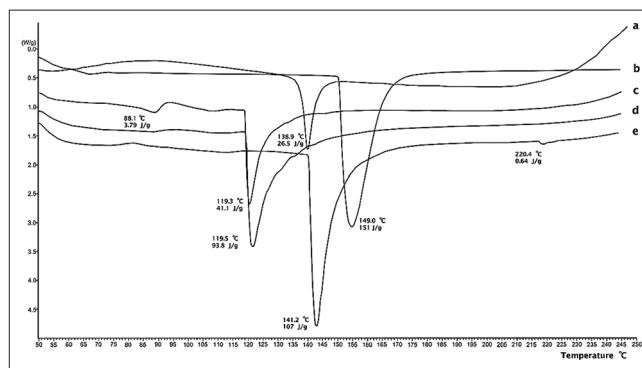
Results of thermal analysis by DTA of intact efavirenz, PVP K-30, and solid dispersions are shown in Figure 3. Efavirenz has a melting point of 138.9°C, whereas the water loss temperature of PVP K-30 was 149°C. The solid dispersion samples with a ratio of 1:2 had two peaks points which were at 88°C and 119.3°C. In contrary, the solid dispersion at ratio 1:1 and 2:1 had only one point, which was 119.5°C and 141.2°C, respectively.

### Fourier transform infrared spectroscopy analysis

Results of the analysis by FT-IR intact efavirenz, PVP K-30, and solid dispersion efavirenz – PVP K-30 can be seen in Figure 4. Efavirenz has N-H bond at wavenumber 3314.82  $\text{cm}^{-1}$ , whereas solid dispersions at ratio 2:1; 1:1, and 1:2 showed a shift toward wavenumber 3251.67  $\text{cm}^{-1}$ , 3256.71  $\text{cm}^{-1}$ , and 3433.56  $\text{cm}^{-1}$ , respectively.



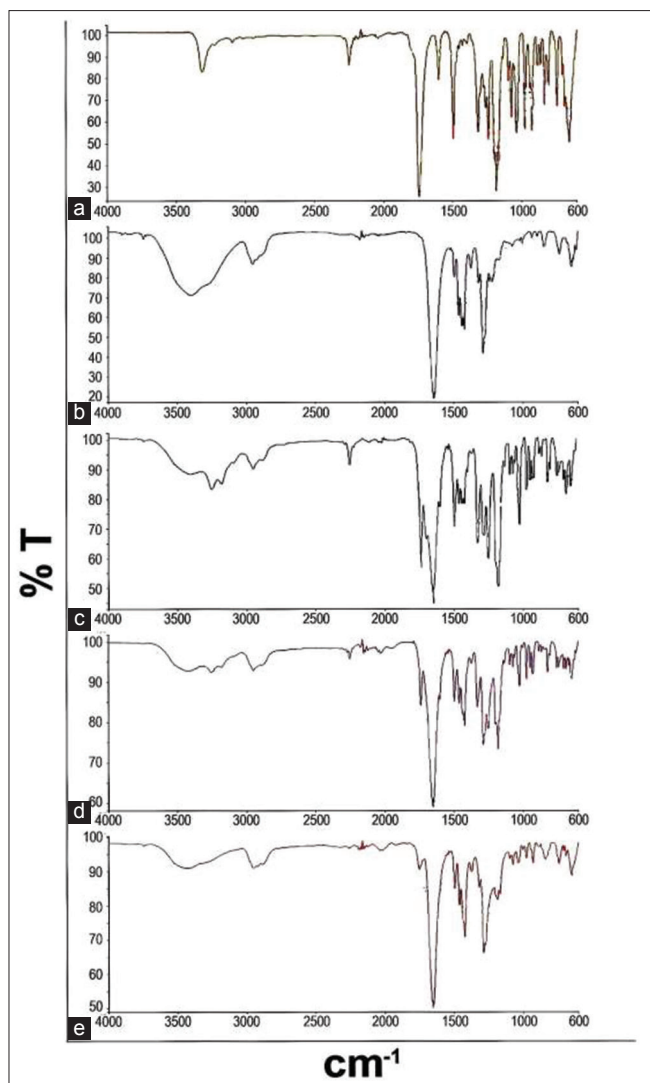
**Figure 2:** Powder X-ray diffractogram of A: intact efavirenz, B: solid dispersion at ratio 2:1, C: solid dispersion at ratio 1:1 D: solid dispersion at ratio 1:2 and E: polyvinylpyrrolidone K-30



**Figure 3:** Thermogram differential thermal analysis a: intact efavirenz, b: polyvinylpyrrolidone K-30, c: solid dispersion at ratio 2:1, d: solid dispersion at ratio 1:1 and e: solid dispersion at ratio 1:2

### Solubility test

The solubility test result of intact efavirenz and solid dispersion efavirenz – PVP K-30 was expressed in the levels



**Figure 4:** Fourier transform infrared spectrum of a: intact efavirenz, b: polyvinylpyrrolidone K-30, c: solid dispersion at ratio 2:1, d: solid dispersion at ratio 1:1 and e: solid dispersion at ratio 1:2

of dissolved drug in the saturated condition. The solubility efavirenz and solid dispersion efavirenz – PVP K-30 at different ratios can be seen in Table 1.

## DISCUSSION

One of the anticipated impacts on solid dispersion formulation using polymer is a transformation from a crystalline phase into amorphous phase.<sup>[13]</sup> According to the SEM result as shown in Figure 1, the morphology of the solid dispersion efavirenz – PVP K-30 at different ratio showed an obvious difference compared to intact efavirenz which depicted a polyhedral rod-shaped crystal habit, whereas PVP K-30 is irregular round shape on its surface. This result likely indicated a transformation from crystalline to amorphous phase.

The degree of crystallinity can be observed by the X-ray diffraction analysis.<sup>[14]</sup> As shown in Figure 2, solid dispersion

**Table 1: Solubility test of intact efavirenz and solid dispersion of efavirenz – polyvinylpyrrolidone K-30**

Materials	Solubility ( $\mu\text{g/mL}$ )
Intact efavirenz	$0.250 \pm 0.047$
Solid dispersion (2:1)	$6.777 \pm 0.113$
Solid dispersion (1:1)	$6.936 \pm 0.026$
Solid dispersion (1:2)	$14.672 \pm 0.416$

at ratio 2:1 had a higher degree of crystallinity, which likely due to the concentration of PVP K-30 was not sufficient to entrap the efavirenz crystal in the solid dispersion system. At higher concentration of PVP K-30, 1:1 and 1:2, PVP K-30 was able to cover efavirenz crystal in the form of solid dispersion. Thus, the crystallinity degree of solid dispersion decreased with the increasing in the concentration of polymer.

In accordance with the X-ray diffraction analysis, the thermal analysis showed that solid dispersion sample at ratio of 2:1 had two peaks point at  $88^\circ\text{C}$ , which indicated the glass transition temperature of PVP K-30, and at  $119.3^\circ\text{C}$  which was expected to be partial transformation from crystalline phase to amorphous phase of solid dispersion. Moreover, solid dispersion at ratio 1:1 and 1:2 had only one point that indicated the physical interaction of the two substances is likely due to the formation of the amorphous phase in solid dispersion. The endothermic peaks of solid dispersion showed an increasing trend correspond to the increasing amount of PVP K-30.

Spectroscopy infrared analysis was done to investigate the shift of the spectrum formed from efavirenz and PVP K-30 to solid dispersion due to hydrogen bonding or Van der Waals bonding. Hydrogen bonding can occur when atom H meets atom N and forms N-H bond. In the spectroscopy infrared, N-H bond is usually seen in the wave number  $3060\text{--}3500\text{ cm}^{-1}$ . Results of this analysis indicated the shift of N-H bond, which likely occur due to the formation of hydrogen bond between efavirenz and PVP K-30 in solid dispersion. In addition, this result supports the results of the previous analysis that the solid dispersion shows a shift change in the crystal structure of the drug in the solid dispersion.

The solubility results of solid dispersion efavirenz – PVP K-30 increased significantly ( $P < 0.05$ ) at different ratios, as shown in Table 1. Moreover, the influence of PVP K-30 concentration can also be seen that the greater the concentration of PVP K-30 given the greater solubility. This result is accordance with previous inspections, which the X-ray diffraction analysis showed a decline in the degree of crystallinity thus the number of efavirenz dissolved is greater.<sup>[12,15]</sup> The FT-IR spectroscopy results also support the solubility result, the hydrogen bonds which likely were formed will facilitate the drug molecules when in contact with water during the tests solubility.

## CONCLUSIONS

Efavirenz and PVP K-30 can be prepared as solid dispersion at different ratios and showed changes in the characteristic that seen in the morphology, degree of crystallinity, thermal behavior, and infrared spectroscopy. The effect of PVP K-30 concentration gives a significant contribution in the increasing the solubility of efavirenz, which the solid dispersion of efavirenz at ratio 1:2 showed the highest solubility.

## Acknowledgment

The authors would like to thank Dr. Dwi Setyawan from Airlangga University for providing thermal analysis DTA in this research.

## Financial support and sponsorship

Nil.

## Conflicts of interest

There are no conflicts of interest.

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